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EXAMINER

SHAHNAN SHAH, KHATOL S

ART UNIT

PAPER NUMBER

1645

DATE MAILED: 09/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary**Application No.**

09/942,024

Applicant(s)

STEWART ET AL.

Examiner

Khatol S Shahnan-Shah

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 July 2004 and 06 August 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 35-53 is/are pending in the application.
- 4a) Of the above claim(s) 37 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 35,36 and 38-53 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 19 July 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 8/6/04.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 7/19/04 has been entered.
2. Applicants' amendments and response of 7/19/04 are acknowledged. Claims 39 and 40 have been amended.
3. Claims 35-53 are pending. Claim 37 is withdrawn as being drawn to non-elected invention.
4. Claims 35-36 and 38-53 are under consideration.

Prior Citations of Title 35 Sections

5. The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior office action.

Prior Citations of References

6. The references cited or used as prior art in support of one or more rejections in the instant office action have been previously cited and made of record. No form PTO-892 has been submitted with this office action.

Drawings

7. Objection to the drawings made in paragraph 5 of the office action mailed September 23, 2003 is withdrawn. Applicants have submitted formal drawings on 7/19/04. The drawings have been accepted by the examiner.

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Objections Withdrawn

8. Objections to claims 39-40 made in paragraph 7 of the office action mailed September 23, 2003 are withdrawn in view of applicants' amendments.

Rejections Maintained

9. Rejection of claims 35, 36, 38, 39, 41, 42, 44, 45, 47, 48 and 53 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 61, 62, 63, 67, 71, 72, 73, 74, 76, 77, 78, 79, 80, 81, and 82 of copending Application No. 10261161 made in paragraph 9 of the office action mailed September 23, 2003 has been maintained. No terminal disclaimer has been submitted by the applicants.

10. Rejection of claims 35- 36 and 38-53 under 35 U.S.C. 103(a) made in paragraph 15 of the office action mailed September 23, 2003 has been maintained.

The rejection was as stated below:

Claims 35-36 and 38-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al. (US 5,965,699) in view of Clegg (Current Opinion in Biotechnology Vol. 6, pp 103-110, 1995).

Claims are drawn to a method of determining protease activity using fluorescence resonance energy transfer.

Schmidt et al. teach a method of determining protease activity using a labeled based assay (see abstract and claims). Schmidt et al. teach a botulinum toxin substrate and BoNT A peptide sequence (see claim 1). Schmidt et al. also teach BOTOX (see column 12, lines 15-20). Schmidt et al. teach detecting increase or decrease protease activity (see claim 9) and

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comparing the activity to a control. Schmidt et al. teach using fluorescamine as a fluorophore. Schmidt et al. do not teach FRET. However, Clegg teaches utility of fluorescence resonance energy transfer in biological assays and for study of enzymes (see abstract and page 106 under biotechnological applications).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the method taught by Schmidt et al. with well known FRET method taught by Clegg to obtain the claimed method.

One having ordinary skill in the art would have been motivated by the teachings of Clegg that FRET assays can be exploited for fluorometric enzyme assays. (see page 106 under biotechnological applications) to use FRET assay for determining protease activity of botulinum toxins.

Applicants arguments of 7/19/04 have been fully considered but they are not persuasive. Applicants argue that the claimed methods are unobvious over Schmidt et al. in view of Clegg. Applicants further argue specifically Schmidt et al. describe a method of labeling BoNT/A cleavage product for quantitation of BoNT/A but, neither Schmidt et al. alone nor in combination with Clegg, teach or suggest resonance energy transfer assay for determining protease activity of BoNT/A.

In response to applicants' argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge

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generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to modify the assay of Schmidt by incorporating FRET comes from the teaching of Clegg “ The benefits of fluorescence resonance energy transfer are becoming increasingly evident to researchers who require measurements with high sensitivity, specificity, noninvasiveness, rapidity and relative simplicity” see abstract. Clegg also teaches that in another study, FRET has been employed to observe the toxic effects of cytolytic toxins (see page 104).

Applicants admit that the general advantages of FRET described in Clegg review have been available since 1995. Therefore, one having ordinary skill in the art would have been motivated by the teachings of Clegg that FRET assays can be exploited for fluorometric enzyme assays. (see page 106 under biotechnological applications) to use FRET assay for determining protease activity of botulinum toxins.

New Rejection

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 35-36 and 38-47 are rejected under 35 U.S.C. 102(e) as being anticipated by Schmidt et al. (US 6,762,280). Prior art of record.

The claims are drawn to a method of determining protease activity of botulinum toxin serotype A.

Schmidt et al. discloses a method of determining protease activity of botulinum toxin serotype A see claims specially claims 2-3, 6-7 and 9. Schmidt et al. discloses substrates for clostridial neurotoxins and that these substrates can be modified peptides or proteins that can serve as FRET substrates (abstract; col. 4). Schmidt et al discloses that Botulinum serotype A cleaves the protein SNAP-25 and that because botulinum neurotoxins are proteases, practical assays for this activity could form the basis for detection, quantification and drug-screening systems (col. 1). Schmidt et al discloses substrate peptides suitable for use in fluorescence resonance energy transfer assays (FRET), also known as quenched-signal assays, for the protease activities of clostridial neurotoxins (col. 3). Schmidt et al discloses "FRET substrates for proteolytic activities of clostridial neurotoxins. Each contains a fluorescent group (fluorophore) on one side of the cleavage site, and a molecule that quenches that fluorescence on the other side of the cleavage site. Upon neurotoxin-catalyzed hydrolysis, the fluorophore and quencher diffuse away from each other, and the fluorescence signal increases in proportion to the extent of hydrolysis." (col. 5; see also col. 7). Schmidt et al teach comparing fluorescence from the sample with a control (see claim 9). The prior art anticipates the claimed invention.

Conclusion

11. No claims are allowed.
12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol S Shahnan-Shah whose telephone number is (571)-272-0863. The examiner can normally be reached on 7:30am-4 pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette F Smith can be reached on (571)-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

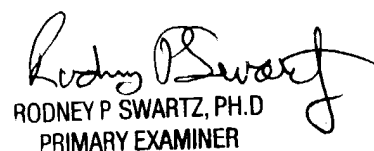


Khatol Shahnian-Shah, BS, Pharm, MS

Biotechnology Patent Examiner

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September 17, 2004



RODNEY P. SWARTZ, PH.D.
PRIMARY EXAMINER